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Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02016944.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Anmeldung Nr:
Application no.: 02016944.7
Demande no:

Anmeldetag:
Date of filing: 01.08.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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,
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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Process for the manufacture of 3-amino-pyrrolidine derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D207/00

An Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

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Case 21296

Process for the manufacture of 3-Amino-pyrrolidine Derivatives

The present invention is concerned with a novel process for the manufacture of racemic and optically active 3-amino-pyrrolidine derivatives and with the use of this process for the production of cephalosporin derivatives.

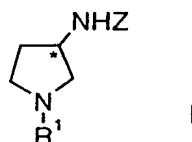
5 3-Amino-pyrrolidine derivatives, especially optically active 3-amino-pyrrolidine derivatives, are important intermediates for the production of agrochemicals and of pharmaceutically active substances such as, for example, of vinylpyrrolidinone-cephalosporin derivatives.

10 3-Amino-pyrrolidine derivatives can be manufactured in a manner known per se, for example as described in EP-A-0 218 249 starting from 1,2,4-trisubstituted butane derivatives such as e.g. tribromobutane or trihydroxybutane. The racemic derivatives can then, if desired, can be converted by a racemate resolution into optically active 3-amino-pyrrolidine derivatives, JP 09124595-A. A process for the manufacture of optically active 3-amino-pyrrolidine derivatives based on the conversion of 4-hydroxy-proline as described,
15 for example, in J. Med. Chem. 1764(92), 35, gives optically active 3-aminopyrrolidine over 3 steps.

20 The known methods for the manufacture of 3-aminopyrrolidine derivatives as described, for example, in UK Patent No. 1 392 194, EP-A-0 391 169 and US Patent No. 4 916 141, are time consuming and lead to expensive intermediates. The interest in other processes for the manufacture of 3-amino-pyrrolidine derivatives, especially of optically active 3-amino-pyrrolidine derivatives, is therefore extremely high. Thus, Tomori et al. (Heterocycles, 1997, 1, 213-225) have synthesised (S)-3-(t-butoxycarbonylamino)-pyrrolidine from (S)-3-benzyloxycarbonylamino-1,4-dimethanesulfonyloxybutane by cyclization with excess allylamine and deallylation of the resulting (S)-1-allyl-3-

(benzyloxycarbonylamino)pyrrolidine with palladium on charcoal. However, on a technical scale allylamine is unpractical, being a poisonous, inflammable and explosive liquid; also, palladium is an expensive catalyst. It was now found that 3-amino-pyrrolidine derivatives, especially optically active 3-amino-pyrrolidine derivatives, can be safely
5 manufactured in high yield on a technical scale by replacing allylamine with hydroxylamine or its acid addition salt, particularly the hydrochloride, which is cheap and much easier to handle, having none of the said disadvantages, being a solid, which is easily soluble in polar organic solvents such as tetrahydrofuran, ethanol, triethylamine or mixtures thereof. The hydroxy group of the resulting N-hydroxy-3-protected-amino-
10 pyrrolidine is then removed by catalytic reduction with Raney nickel, which is a cheap catalyst.

In accordance with these findings, the invention is concerned with a process for the manufacture of 3-amino-pyrrolidine derivatives of the formula



15 wherein

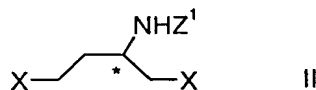
R¹ signifies hydrogen or an amino protecting group;

Z signifies hydrogen or an amino protecting group;

and

* represents a center of chirality,

20 which process comprises converting a compound of the formula



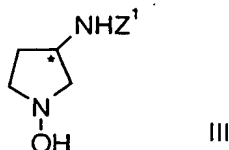
wherein

X signifies a protected hydroxy group;

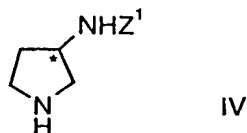
Z¹ signifies an amino protecting group; and

25 * has the above meaning,

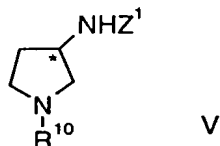
in the presence of hydroxylamine or an acid addition salt thereof into the N-hydro-pyrrolidine derivative of the general formula



wherein Z^1 and * have the above meanings,
the N-hydroxy group of which is subsequently reduced to the secondary amine of the
general formula

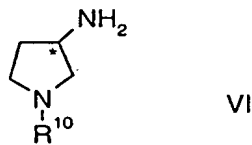


5 wherein Z^1 and * have the above meanings,
by hydrogenation with Raney nickel; and, if desired, protecting the secondary N^1 amino
group by reaction with a compound of the formula $R^{10}X^1$, in which R^{10} is an amino
protecting group and X^1 is halogen or a leaving group, to yield a compound of the general
formula



10

in which R^{10} , Z^1 and * have the above meanings,
and, if desired, deprotecting the secondary 3-amino group by catalytic hydrogenation to
yield a compound of the general formula



15 in which R^{10} and * have the above meanings.

Under the above definitions the term "protected hydroxy group" in the scope of the
present invention encompasses ester groups, for example, sulfonates such as mesylate,
tosylate, p-bromobenzenesulphonate or p-nitrobenzenesulphonate. These are especially
groups which are cleaved off selectively under the reaction conditions for the ring closure
20 such that the amino protecting group Z in the 2-position is not liberated. Mesylate and
tosylate (mesyloxy and tosyloxy) are especially preferred protected hydroxy groups X.

The term "amino protecting group" in the scope of the present invention
encompasses lower alkyl, benzyl, lower alkenyl, lower alkoxy carbonyl, lower alkenyl-
oxy carbonyl, benzyloxy carbonyl and the like. t-Butoxy carbonyl, allyloxy carbonyl and
25 benzyloxy carbonyl, particularly the latter, are especially preferred.

The term "leaving group" embraces halogen atoms, such as chlorine or bromine, and lower alkylsulfonyloxy or lower alkylphenylsulfonyloxy groups such as mesyloxy or tosyloxy, also anhydride residues of carbonic acid such as t-butoxycarbonyloxy.

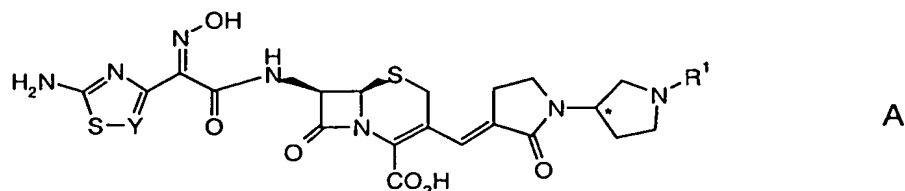
The term "lower alkyl" in the scope of the present invention encompasses straight-chain and branched, optionally chiral hydrocarbon groups with 1 to 8 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, i-propyl, i-butyl, tert-butyl, 2-methylbutyl and the like. "Lower alkoxy" has analogous significance.

The term "lower alkenyl" encompasses olefinic, straight chain and branched groups with 2 to 8 carbon atoms such as vinyl, allyl, 3-butenyl, 1,3-butadienyl.

The terms "lower allyl", "lower alkoxy" and "lower alkenyl" keep their meanings in combinations e.g. with "carbonyl", e.g. t-butoxycarbonyl, allyloxycarbonyl.

In an especially preferred aspect of the process of the present invention optically active R-form of 2-(benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane is cyclized with hydroxylamine hydrochloride at about 0°C to the boiling point of the reaction mixture in a polar solvent such as tetrahydrofuran, ethanol, triethylamine or dimethylsulfoxide or a mixture thereof, quite preferably in triethylamine. Subsequently, the hydroxy group of the resulting N-hydroxy-3-protected pyrrolidine of formula III is reductively removed by hydrogenation with Raney nickel at room temperature in a hydrogen atmosphere. The resulting secondary amine of formula IV can subsequently be N-protected, preferably by t-butoxycarbonyl, by reaction with di-t-butyl-dicarbonate, preferably at room temperature. The benzyloxycarbonyl protecting group of the resulting di-protected product of formula V is expediently removed catalytically with hydrogen and palladium on charcoal, preferably at room temperature.

The resulting primary amine of formula VI is especially suitable for manufacturing vinylpyrrolidinone-cephalosporin derivatives of the general formula



wherein

Y signifies CH or nitrogen;

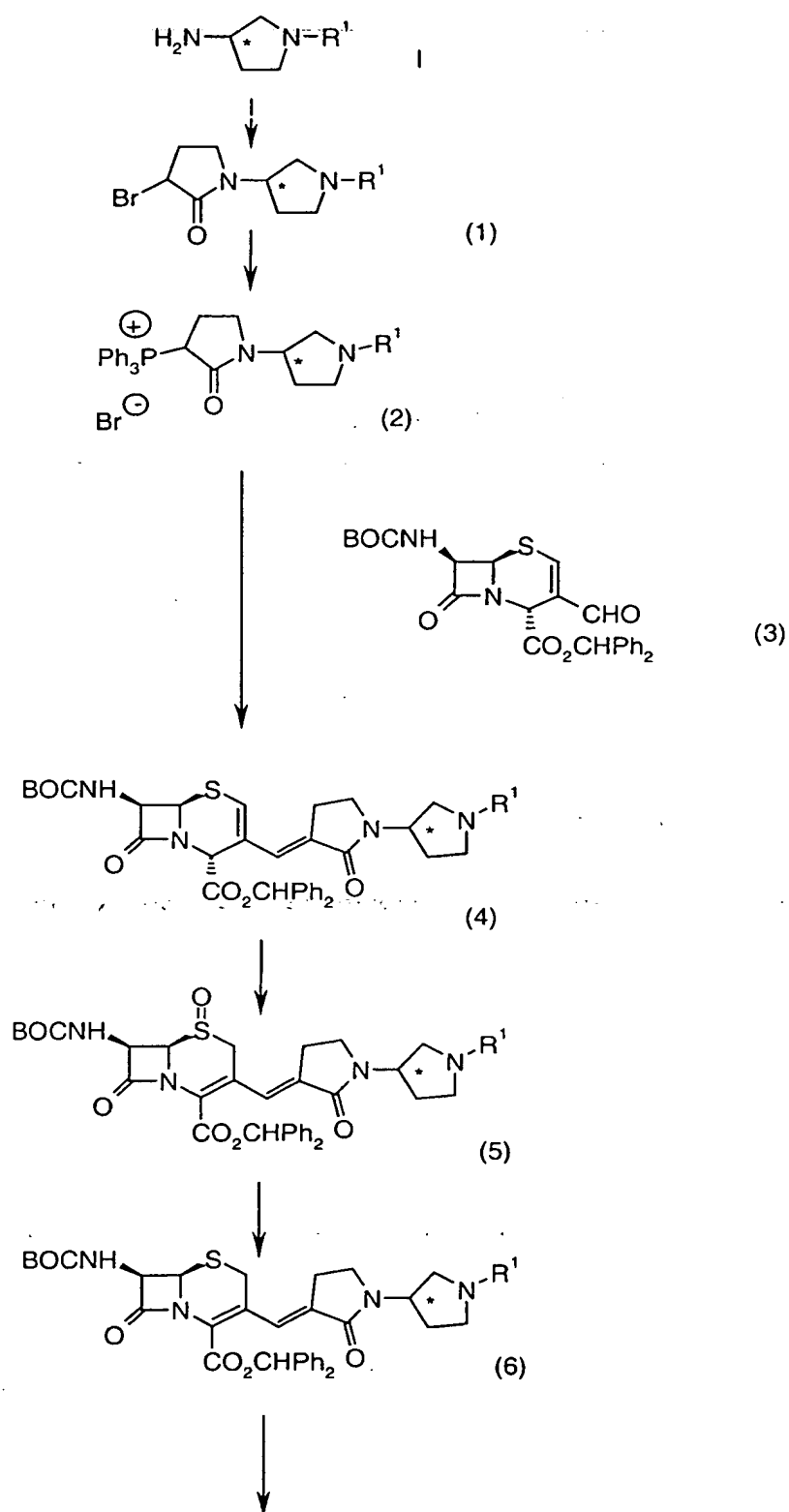
R¹ denotes hydrogen or an amino protecting group; and

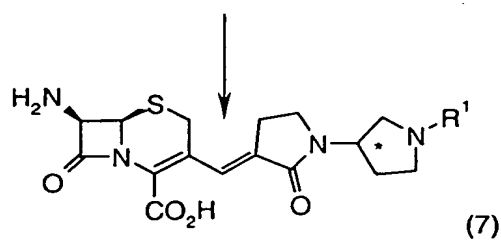
* denotes a center of chirality.

Compounds of formula A are cephalosporin derivatives having a high antibacterial activity, especially against methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.

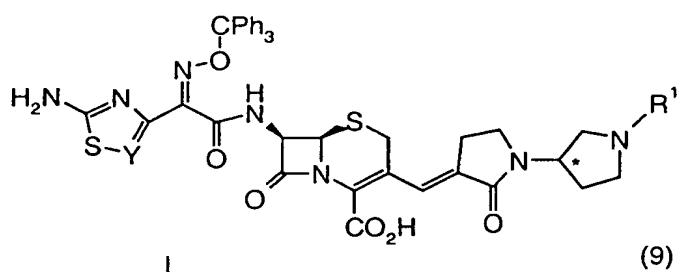
Compounds of the general formula A can be produced as per EP-A-849 269 in
5 accordance with Scheme I:

Scheme 1

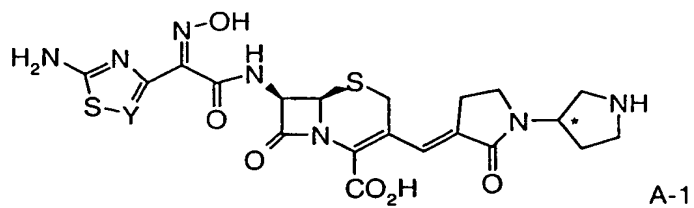
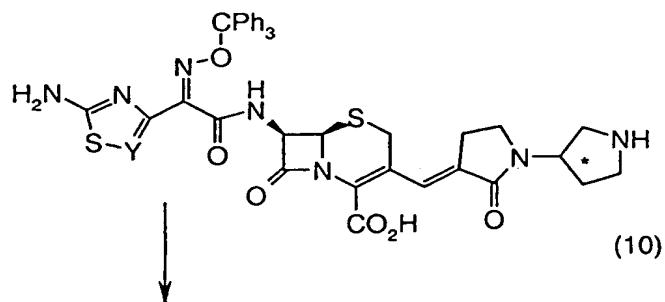




Acylation with (Z)-(5-amino[1,2,4]thia(dia)zol-3-yl)-trityloxyimino-thioacetic acid S-benzothiazol-2-yl ester



removal of protection group R¹



In Scheme 1 Y, R¹ and * have the above significance; Ph is phenyl, BOC is t-butoxy-carbonyl and CHPh₂ is benzhydryl.

For obtaining the compounds of the general formula A the 3-amino-pyrrolidine derivative of formula I are manufactured in accordance with the invention according to the method described above, thereafter reacted in accordance with Scheme 1 with
5 2-bromo-4-chlorobutanoyl chloride, and the N-substituted 3-bromo-2-pyrrolidone (1) so obtained is converted into the Wittig salt (2) which is reacted with the diprotected 3-ene cephalosporin (3). The resulting condensation product (4) is oxidized to the 5-sulfoxide (5) which is reductively isomerized with PBr₃ to the 2-ene cephalosporin (6), the latter is
10 N-deprotected and acylated with the activated acyl derivative (8) to yield (9) which is deprotected in two steps to yield (10) and finally the end product of formula A.

The following Examples serve to illustrate the invention.

Example 1

(R)-3-(Benzyloxycarbonylamino)-N-hydroxy-pyrrolidine.

15 (R)-2-(Benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane (2.0 g; 5.06 mmol) was dissolved in a Et₃N/DMSO mixture (1:1, 20 ml). Hydroxylamine hydrochloride (1.4 g; 20.2 mmol) was added and the mixture was heated at 60°C over night. The mixture was poured in aqueous HCl (the pH was adjusted to pH=6 with NaHCO₃) and extracted twice with AcOEt. The organic phase was washed with water and
20 dried over Na₂SO₄. The solids were filtered off and the solvent was removed. A light yellow oil (1.4 g, purity 73%) was obtained (yield: 85%). The crude title compound was used as is.

Example 2

(R)-3-(Benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine.

25 The crude (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine obtained above (1.4 g) was dissolved in ethanol (10 ml). Raney nickel (about 2 g) was added to this mixture. The reaction was degassed under reduced pressure and hydrogen supply (three times) and subsequently put under hydrogen atmosphere (1 bar). The reaction was over after 6 hours, yielding crude (R)-3-(benzyloxycarbonylamino)-pyrrolidine which was
30 further processed in situ, in that di-tert-butyl dicarbonate (1.0 g, 4.58 mmol) was added; the mixture was stirred for one hour. The solvent was removed and the residue taken up in an n-hexane/AcOEt mixture (1:1, 20 ml) and filtered through a silicagel pad. The silica was washed with n-hexane/AcOEt mixture (1:1; 250 ml). The organic phases were evaporated.

The compound was obtained as a colorless oil (1.125 g; yield 81%) in good purity, i.e. at least 90 - 95 %, rendering the compound sufficiently pure for further reaction, e.g. in Example 3.

NMR: (CDCl₃; 300 MHz): 7.34 (m; 5H); 5.1 (s(broad); 2H); 4.83 (m(broad); 1H); 4.22 (m(broad); 1H); 3.60 (dd; 1H); 3.41 (m(broad); 2H); 3.18 (m(broad); 1H); 2.12 (m; 1H); 1.82 (m(broad); 1H); 1.45 (s; 9H).
MS: (M+H⁺): 321.3 (M+NH₄⁺): 338.2

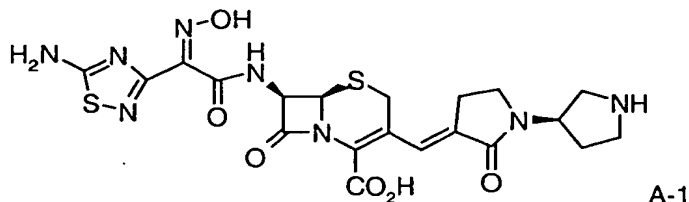
Example 3

(R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine.

(R)-3-(Benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine (300 mg) was dissolved in ethanol (5 ml). Palladium on charcoal 10% (20 mg) was added. The reaction was degassed three times and put under hydrogen atmosphere (1 bar). The reaction was over after 2 hours. The solvent was removed, the residue was taken up in ethyl acetate (5 ml) and filtered through a silica gel pad. The silica was washed with ethyl acetate (50 ml). The organic phases were evaporated. The desired (R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a colourless oil in a quantitative yield (175 mg).

NMR: (CDCl₃; 300 MHz): 3.6-3.3 (m(broad); 3H); 3.05 (m(broad); 1H); 2.29 (s(broad); 2H); 2.05 (m; 1H); 1.66 (m(broad); 1H); 1.46 (s; 9H).
MS: (M+H⁺): 187.3

The (R)-3-amino-N-(t-butoxycarbonyl)-pyrrolidine can be utilized in Example 2 of EP-A-0 849 269 instead of the N-allyloxycarbonyl derivative and subsequently in Examples 3-11 to yield (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid of the formula



Example 4

A 200 l reactor was charged with 27 l of dimethylsulfoxide, 9.5 kg of (R)-2-(benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane and 6.68 kg of hydroxylamine hydrochloride and the reaction mixture stirred at room temperature to

suspend. 27 l of triethylamine were added slowly, whereupon the temperature rose to 45 - 50 °C. The reaction mass was maintained at 55 °C for four hours. The reaction was monitored by NMR or HPLC (high performance liquid chromatography). Subsequently the reaction mixture was cooled to room temperature.

5 Separately a solution was prepared with 100 l of water at 0 °C containing 14.2 l of concentrated aqueous hydrochloric acid. The above reaction mass was added to this solution and the pH value checked to 1.0 to 1.5. The aqueous layer was washed twice with each 10 l of 1:1 ethyl acetate and n-hexane and neutralized with 15 kg of sodium
10 bicarbonate. The reaction mixture was stirred for 30 minutes and the pH checked to about 7.0 - 7.5. The aqueous layer was extracted three times with 15 l of ethyl acetate each time. The combined organic phases were washed twice with each 15 l of water followed by 10 l of brine (saturated aqueous sodium chloride solution).

The solvent was evaporated at reduced pressure, at the end of which the oily residue was stripped with 10 l of n-hexane. The n-hexane was evaporated off, n-hexane added
15 again and the mixture stirred to precipitate the product. The crude (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine was filtered off and used directly in example 5. The white solid obtained changed to yellow upon storage.

Yield 4.6 - 5.0 kg (80 - 85 %) having a purity of more than 95 %.

Example 5

20 A 50 l autoclave was charged with 22.5 l of ethanol, 4.5 kg of (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine and 1.35 kg of Raney nickel. The autoclave was put under hydrogen atmosphere (50 psi = 3.5 bar) and stirred for four hours. The reaction was monitored by HPLC and TLC.

After reaction the catalyst was filtered off and the solvent removed by evaporation at
25 reduced pressure. The residue, crude (R)-3-(benzyloxycarbonylamino)-pyrrolidine, was dissolved in 20 l of ethanol followed by 4.15 kg of di-tert-butyl dicarbonate. The reaction mixture was stirred at room temperature for two hours, the reaction being monitored by HPLC and TLC. The solvent was evaporated off at reduced pressure, the reaction mixture being stripped twice by the addition of 2 l of toluene each time.

30 5.7 kg of crude (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a yellowish oily residue, which was purified by dissolution, in a 20 l reactor, in 11.4 l of methylene chloride followed by 2.85 kg of silica gel and 57 g of charcoal. The reaction mixture was stirred for two hours at room temperature. The solids were filtered off and washed thoroughly with 10 l of methylene chloride. The combined

organic layers were evaporated at reduced pressure, yielding 5.1 kg of (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine as a colourless oil.

Example 6

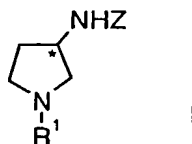
An autoclave was charged with 51 l of ethanol, 5.1 kg of (R)-3-
5 (benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine, 0.51 g of 5 % palladium-on-carbon and 0.5 l of perchloric acid. The autoclave was put under hydrogen atmosphere (100 psi = 7 bar) for one hour, the reaction being monitored by NMR. After completion of the reaction the catalyst was filtered off and the solvent removed under reduced pressure.

The oily residue was dissolved in 10 l of ethyl acetate and the organic layer washed
10 with 10 l of water, followed by 10 l 10 % aqueous sodium carbonate solution. The organic phase was dried over sodium sulfate and the solvent removed by evaporation under reduced pressure. 2.5 kg of (R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a colourless oil. The NMR spectrum is identical with that reported under Example 3.

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Claims

1. A process for the manufacture of 3-amino-pyrrolidine derivatives of the formula



wherein

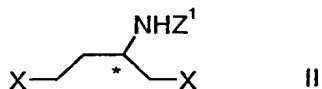
5 R¹ signifies hydrogen or an amino protecting group;

Z signifies hydrogen or an amino protecting group;

and

* represents a center of chirality,

which process comprises converting a compound of the formula



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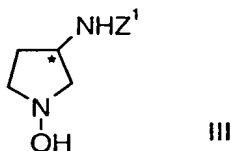
wherein

X signifies a protected hydroxy group;

Z¹ signifies an amino protecting group; and

* has the above meaning,

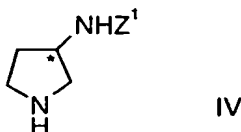
15 in the presence of hydroxylamine or an acid addition salt thereof into the N-hydroxy-pyrrolidine derivative of the general formula



wherein Z¹ and * have the above meanings;

the N-hydroxy group of which is subsequently reduced to the secondary amine of the

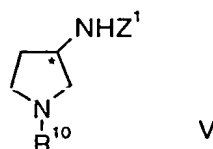
20 general formula



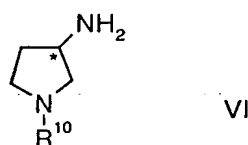
wherein Z¹ and * have the above meanings,

by hydrogenation with Raney nickel; and, if desired, protecting the secondary N¹ amino group by reaction with a compound of the formula R¹⁰X¹, in which R¹⁰ is an amino

protecting group and X^1 is halogen or a leaving group, to yield a compound of the general formula

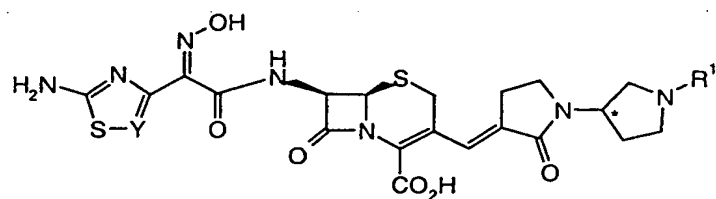


- in which R^{10} , Z^1 and $*$ have the above meanings,
 5 and, if desired, deprotecting the secondary 3-amino group by catalytic hydrogenation to yield a compound of the general formula



in which R^{10} and $*$ have the above meanings.

2. Process according to claim 1, wherein a starting compound of formula II in the
 10 R-form is employed.
3. Process according to claim 1 or 2, wherein a starting compound of formula II, in which X is mesyloxy, is employed.
4. Process according to any one of claims 1-3, wherein a starting compound of formula II, in which Z^1 is benzyloxycarbonyl, is employed.
- 15 5. Process according to any one of claims 1-4, wherein the starting compound of formula II is reacted with hydroxylamine hydrochloride.
6. Process according to any one of claims 1-5, wherein the intermediate of formula IV is reacted with di-tert-butyl-dicarbonate.
7. Process according to any one of claims 1-6, wherein the deprotection of the
 20 secondary 3-amino group of the intermediate of formula V is effected by catalytic dehydrogenation with palladium on charcoal.
8. Process in accordance with any one of claims 1-7, wherein the 3-amino-pyrrolidine of formula I is further processed to a vinylpyrrolidinone-cephalosporin derivative of formula A



A

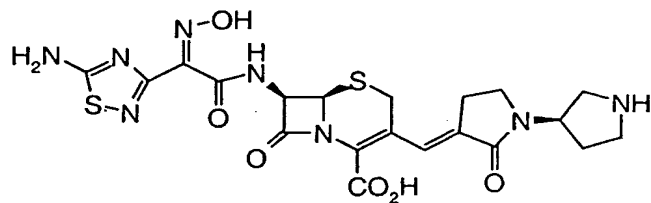
wherein

Y signifies CH or nitrogen;

R¹ denotes hydrogen or an amino protecting group; and

5 * denotes a center of chirality.

9. Process according to claim 8 for the production of (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid of the formula



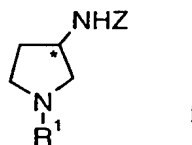
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Abstract

The invention is concerned with a process for the manufacture of 3-amino-pyrrolidine derivatives of the formula



5 wherein

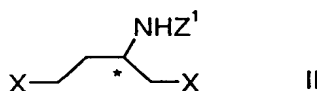
R¹ signifies hydrogen or an amino protecting group;

Z signifies hydrogen or an amino protecting group;

and

* represents a center of chirality,

10 which process comprises converting a compound of the formula



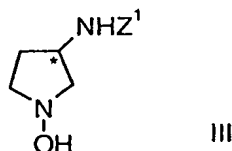
wherein

X signifies a protected hydroxy group;

Z¹ signifies an amino protecting group; and

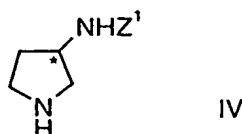
15 * has the above meaning,

in the presence of hydroxylamine or an acid addition salt thereof into the N-hydro-pyrrolidine derivative of the general formula



wherein Z¹ and * have the above meanings;

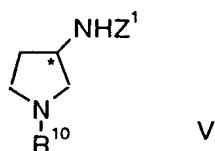
20 the N-hydroxy group of which is subsequently reduced to the secondary amine of the general formula



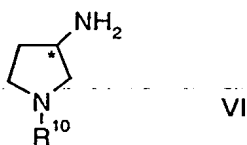
wherein Z¹ and * have the above meanings,

by hydrogenation with Raney nickel; and, if desired, protecting the secondary N¹ amino
25 group by reaction with a compound of the formula R¹⁰X¹, in which R¹⁰ is an amino

protecting group and X^1 is halogen or a leaving group, to yield a compound of the general formula



- in which R^{10} , Z^1 and $*$ have the above meanings,
- 5 and, if desired, deprotecting the secondary 3-amino group by catalytic hydrogenation to yield a compound of the general formula



in which R^{10} and $*$ have the above meanings.

Also of concern is the further processing of compound I to vinylpyrrolidinone-
10 cephalosporin derivatives.